Nodal involvement evaluation in advanced cervical cancer: a single institutional experience

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Summary

Purpose: To assess the usefulness of different imaging techniques in the detection of nodal involvement in patients with advanced cervical carcinoma. Moreover, to analyze the correlation between the presurgical (FIGO) and postsurgical (pTNM) staging classifications. *Materials and Methods:* All patients diagnosed with advanced cervical cancer (FIGO Stages IIB-IV) from 2005 to 2012 were selected. The medical charts of 51 patients that underwent presurgical assessment with posterior surgical staging by means of para-aortic lymphadenectomy, were reviewed. Nodal status assessment by computed tomography scan (CT scan), magnetic resonance imaging (MRI), positron emission tomography (PET), and sonography was compared, as well as the size given in imaging techniques compared to the final pathologic report information. *Results:* Presurgical analysis by CT scan, MRI, PET, and sonography showed pelvic nodal involvement in 51.3% of patients, and para-aortic involvement in 30.8% of cases. CT scan showed positive pelvic nodes in 35% of cases, but pathologic confirmation was observed in just 17.6% of cases. However, MRI resulted in higher rates of up to 48.8% of cases. Concerning para-aortic nodal involvement, CT scan showed positive nodes in 25% of cases, MRI in 3.2% of cases, and the pathologic report in 15.6% of cases. The authors found significant differences between staging groups among both classifications (FIGO vs. pTNM; $p < 0.001$). Eight cases (15.7%) were understaged by FIGO classification. *Conclusions:* Despite all imaging techniques available, none has demonstrated to be efficient enough to avoid the systematic study of para-aortic nodal status by means of surgical evaluation.

Key words: Cervical cancer; Staging; Imaging techniques; Lymphadenectomy; Nodal involvement; Extraperitoneal.

Introduction

Cervical cancer is the second malignancy according to frequency around the world [1]. The incidence of cervical cancer is even greater in developing countries, and it is the first cause of death due to cancer [2]. Prognosis is directly related to the tumor stage at diagnosis, and despite the efforts for an early diagnosis, 25% of cases are diagnosed at an advanced stage.

The accepted classification for cervical cancer is the one proposed by FIGO [3], although it does not consider imaging tests and nodal involvement. Postsurgical staging or pTNM [4] is the most accurate approach for valuing the stage, since it determines nodal involvement more accurately. Up to 26% of women without evidenced disease in the presurgical study show postsurgical para-aortic involvement [5]. This underestimate of tumor stage could modify the planned treatment in up to 40% of patients [6], thus a correct assessment of the spread of the disease is essential.

Five-year overall survival is estimated at 85%-90% when nodal involvement is negative, dropping to 20%-75% when positive. This is the main reason to consider nodal metastasis the most important prognostic factor for these patients [7]. The gold standard to assess nodal involvement is to perform a para-aortic lymphadenectomy, and the extraperitoneal approach seems to be the most appropriate when nodal involvement is suspected [8, 9]. However, if the pathologic study of para-aortic nodes is not feasible, imaging tests will be chosen. Available choices include magnetic resonance imaging (MRI), abdominal/pelvic computed tomography (CT) scan, and positron emission tomography (PET). Each one presents different advantages and disadvantages.

The aim of this study was to assess the usefulness of different imaging techniques in the detection of nodal involvement in patients with advanced cervical carcinoma, and their correlation with actual involvement by means of their pathological assessment. The second objective was to analyze the correlation between presurgical (FIGO) and postsurgical (pTNM) staging classifications.

Materials and Methods

After obtaining approval from the Institutional Review Board approval, the medical charts of all patients diagnosed with advanced cervical cancer (FIGO Stages IIB-IV) [3], from January 2005 until December 2010 at the gynecologic oncology unit of La Paz University Hospital in Madrid, were reviewed. Pathologic confirmation was required. The authors excluded FIGO Stage IVB cases, since no follow-up of these patients was available.

Data collected included: patient's age, presurgical FIGO Stage, postsurgical TNM Stage, pathological details, physical exam findings, and metastatic assessment through CT scan, MRI, PET, and sonography.

Patients with suspected advanced cervical cancer underwent presurgical assessment, and later on, the surgical staging was determined by means of para-aortic lymphadenectomy. Surgical staging was systematically conducted in all patients, but especially those with high morbidity. The authors found 40% of patients with surgical staging, since the present department only undertakes this procedure routinely since 2009.

Surgical technique consists of the removal of all the lymph nodes from the common iliac artery to the renal vessels, includ-

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ing those above the inferior cava vein, the interaortocaval, and left para-aortic to the left ureter. All surgeries were performed by the same experienced surgeon. No frozen section intraoperatively analysis was performed, since it would not modify the authors' opinion. Pelvic lymph nodes dissection was only performed when macroscopic nodal involvement was observed.

Nodal status assessment by CT scan, MRI, PET, and sonography was compared, as well as the size given by imaging techniques compared to the final pathologic report. For qualitative variables, the Chi-square test was used. Quantitative variables were compared by the ANOVA test among different imaging techniques. The correlation between quantitative variables was made with the Pearson test. Alpha error was fixed at five percent. Statistical analysis made with the SPSS 15.0 Statistical Package.

Results

Among the 155 patients diagnosed with cervical cancer between January 2005 and December 2010 in the present center, only 51 cases corresponded to locally-advanced FIGO Stages. The average patient age was 54.9 ± 14.6 years.

Most of them (80.4%) were epidermoid carcinomas, 17.6% were adenocarcinomas, and two percent were adenosquamous carcinomas. Regarding the grade of differentiation, the authors observed 10.8% of grade 1, 32.4% of grade 2, and 56.8% of grade 3.

Ten patients (19.6%) underwent pelvic lymphadenectomy, which resulted positive just in one case (10%). The most common surgical route was laparoscopy (77.7%), with an average of 9.1± 4.9 pelvic nodes obtained and an average positivity of two ± 2.4 nodes. Moreover, 20 patients (40.81%) underwent para-aortic lymphadenectomy mostly through laparoscopy (95%). Among them, 68% were through an extraperitoneal approach and 31% through a transperitoneal technique. The authors observed five percent of laparotomies. The average of para-aortic nodes found was 16.7 ± 5.5, with a positivity average of 2.1 ± 3.9 nodes. Forty percent of para-aortic lymphadenectomies were positive.

Table 1 shows the staging according to FIGO [3] and pTNM [4] criteria. The authors found significant differences between staging groups among both classifications ($p < 0.001$). Eight cases (15.7%) were understaged by FIGO classification.

Presurgical analysis by CT scan, MRI, PET, and sonography showed pelvic nodal involvement in 51.3% of patients, and para-aortic involvement in 30.8% of cases. In addition, the authors observed through CT scan cervical thickening in 58.8% of cases, without a clear definition of parametrial involvement. However, MRI was more precise and detailed in describing the uterine cervix and the parametria. Among 25 (49%) positive parametria, CT scan detected seven (25%) cases, while MRI confirmed 14 (56%) of them.

The authors observed a significant linear correlation between the size of tumors measured in the clinical exam and with MRI. The Pearson's correlation was r = 0.7 ($p = 0.01$). PET was only performed in 13.5% of cases in the presurgical evaluation, with cervical positive signal in 100% of them, but negative nodal signal in all cases.

Table 1. — *Contingency table between FIGO and pTNM staging criteria*.

TNM / FIGO	IB2	IIA2	IIB	IIIA	IIIB	IVA	IVB
IB2					1		
IIA2		1					
IIB			10		4	1	
IIIA				4			
IIIB					21		2
IVA						7	
IVB							

Sonographic study provided a description of the uterine cervix, but was unable to assess either pelvis or para-aortic node involvement. It detected parametrial involvement in only five cases (17.24%). In 10.34% cervical atypical vascularization was detected. Incidences of 10.34% and 13.79% of vaginal and bladder infiltrations were found, respectively.

CT scan showed positive pelvic nodes in 35% of cases, but pathologic confirmation was observed just in 17.6% of cases. However, MRI informed of higher rates of up to 48.8% of cases. Concerning para-aortic nodal involvement, CT scan showed positive nodes in 25% of cases, MRI in 3.2% of cases, and the pathologic report resulted in 15.6% of cases (Figure 1).

Discussion

Cervical cancer staging is often based on clinical characteristics through FIGO classification. Although this strategy is usually valid in the assessment of local spread of the disease, it is not valid for nodal involvement or distant assessment. Clinical exam and primary tumor evaluations are the decisive factors to determine if a patient will undergo primary surgery or chemo-radiation therapy as curative treatment. Surgical staging seems to improve the treatment adjustment in comparison to the underestimation caused by FIGO classification [6].

In the present study, the authors observed significant differences ($p < 0.001$) between both staging systems, showing that FIGO classification was understaged in over 15% of patients. Available data published report differences from 25% to 90% of understaging when comparing clinical to surgical staging [10]. On the other hand, FIGO staging does not take into account the use of imaging tests, and thus, it does not consider nodal involvement. Nevertheless, the most important predictor of relapse in patients with cervical cancer is para-aortic lymph node involvement [11]. This could lead to incomplete or incorrect treatment.

Fig. 1

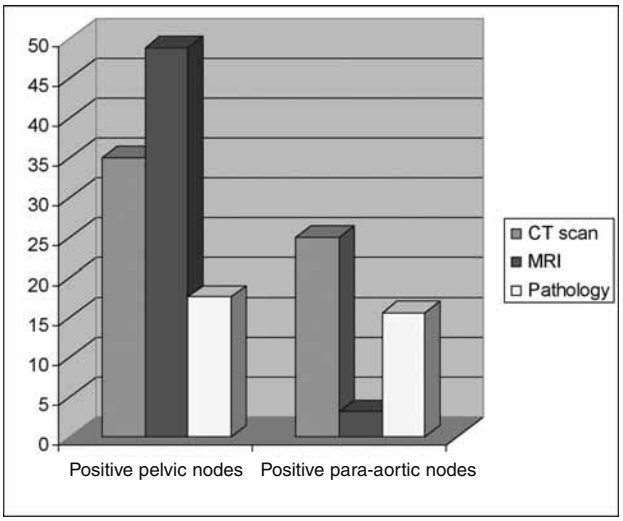

Figure 1. — Comparison between presurgical pelvic and para-aortic nodal involvement through CT scan, MRI, and final histological study.

Currently, para-aortic lymphadenectomy seems to offer better information than imaging studies regarding nodal involvement [9], although there are several reviews that studied the usefulness of imaging techniques in the study of nodal metastases. As a matter of fact, CT scan and MRI are frequently used to evaluate the size of the cervix, to detect positive pelvic or para-aortic lymph nodes, the obstruction of the ureter, and metastasis in the lung or liver. Both imaging tests can detect lymph nodes larger than ten mm which are considered positive, although they are free of tumor in most cases after pathologic exam. In the present series, CT scan detected positive pelvic lymph nodes from five to 40 mm, and para-aortic from ten to 19 mm, while MRI showed positive pelvic nodes from ten to 40 mm (only one histologically involved measuring 23 mm). No significant data in para-aortic lymph nodes was seen and this is perhaps due to a lack of experience of the MRI radiologist in assessing the para-aortic region. This discordance could be caused by nodal hyperplasia, although lymph nodes smaller than 20 mm can contain metastatic disease [9, 12-14].

Bipat *et al*. [13], in a systematic review reported that MRI has greater sensitivity than CT-scan in the study of parametrial invasion, adenopathies characterization, and rectal and bladder involvement. However, both present similar specificity in the detection of adenopathies, because they are based on size. Neither of them detect microinvasion and they show a high rate of false-positives in inflammatory adenopathies. In another study assessing the same aspect, Yang *et al*. [14] also found greater sensitivity for MRI but greater specificity for CT scan, with an overall precision of 89.5% for CT scan and 85.5% for MRI. In the present study, MRI showed higher sensitivity than CT scan in the detection of pelvic adenopathies (48.4% vs 35%, respectively), but both presented a higher false-positive rate in comparison to previously described studies [13, 14].

Regarding para-aortic adenopathies, CT scan once again overestimated nodal involvement, but MRI showed a higher false-negative rate (MRI just detected 3.2% of positive para-aortics while real involvement was 15.6% of cases). The present data contrasts with the published data where MRI outperforms CT scan in the assessment of para-aortic region. Statistical differences ($p < 0.05$) were found among CT scan and MRI.

Besides nodal status, some factors may be taken into account, such as local spread of the disease, tumor size, parametrial infiltration, etc. In this series, MRI outperformed CT scan in parametrial evaluation. Among 25 positive parametria, CT scan detected seven cases while MRI detected 14 of them. Similar results were reported by Yang *et al*. with a sensitivity of 74% and 55% for MRI and CT-scan, respectively [14]. The authors also observed that MRI was the most precise test to assess the size of the uterine cervix, showing a significant Pearson correlation of r = 0.7; similar to data reported in literature [13].

Globally, MRI seems to offer more accuracy in detecting nodal involvement of the disease [13], but it has the great inconvenience of being unsuitable for the virtual simulation and 3D-dosimetry for radiation therapy planning, which only uses CT-scan slides.

Recently, PET has emerged as a technique that allows the assessment of lymph node involvement in patients with uterine cervix carcinoma and does not present the inconvenience of MRI regarding the radiation therapy treatment planning. Since PET is based on physiological processes of cell metabolic activity, it seems more effective than CT scan and MRI for the detection of metastasis in the retroperitoneal area, showing a greater sensitivity and specificity than MRI in the detection of adenopathies [12]. Choi HJ *et al*. [15], compared PET to MRI in the presurgical detection of nodal metastases in patients with FIGO Stages IB-IVA cervical cancer. They observed a precision rate of 72.6% for MRI compared to 85.1% for PET. Sugawara [16] also studied 21 patients with FIGO Stages IB-IVA and observed higher sensitivity for PET compared to CT scan (86% vs 57%, respectively), in the detection of pelvic and para-aortic metastases. On the other hand, both PET and CT scan allow to assess the response to treatment, but PET also seems to be correlated to disease-free survival and overall survival. In fact, some authors consider PET more useful in prognosis than to evaluate lymph node involvement [17, 18].

The authors only performed PET in seven (13.8%) cases due to economical restrictions and to the high work-load on the radiology department. They observed an uptake of 100% at cervical level, and although in literature it is presented as one of the most sensitive and specific tests for the study of adenopathies, the small sample size did not allow them to analyze the metastatic node uptake. Nonetheless, given its high cost and availability only in third-level centers, its use as a routine screen in the study of cervical cancer spread may be questioned.

In a survey conducted among members of the Society of Gynecologic Oncologists in the USA, most of them

did not routinely use PET for the study of presurgical metastasis, although they upheld its great importance in monitoring the response to treatment and follow-up [19].

In conclusion, FIGO classification, in spite of being a valid method for the staging of cervical cancer, showed a higher rate of understaging compared to pTNM classification. Moreover, it does not take into account nodal involvement, which is the most important prognostic factor; but, it could be more useful in developing countries where the lack of resources does not allow a more precise evaluation.

In the authors' opinion, MRI seems to be the most suitable technique for the presurgical evaluation of cervical carcinoma, despite its higher percentage of false negatives in the study of para-aortic area. Moreover, it offers lower cost compared to PET and greater accuracy in pelvic and cervical evaluation compared to CT-scan.

Despite all imaging techniques available, none has demonstrated to be efficient enough to avoid the systematic study of para-aortic nodal status by means of surgical evaluation.

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References

[1] Parkin D.M., Bray F., Ferlay J., Pisani P.: "Estimating the world cancer burden: Globocan 2000". *Int. J. Cancer,* 2001, *94,* 153.

[2] Holschneider C.H.: "Invasive cervical cancer: Epidemiology, clinical features, and diagnosis". In: UpToDate, Basow D.S. (ed.), UpToDate, Waltham, MA, 2008.

[3] FIGO Committee on Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int. J. Gynecol. Obstet.,* 2009, *105*, 103.

[4] Edge S.B., Byrd D.R., Compton C.C., Fritz A.C., Greene F.L., Trotti A. III: "AJCC Cancer Staging Manual: Cervix uteri cancer staging". 7th Ed., New York, Springer, 2010.

[5] Lai C.H., Huang K.G., See L.C., Yen T.C., Tsai C.S., Chang T.C. *et al*.: "Restaging of recurrent cervical carcinoma with dual-phase 18F-fluoro-2-deoxy-D-glucose positron emission tomography". *Cancer*, 2004, *100,* 544.

[6] Gold M.A., Tian C., Whitney C.W., Rose P.G., Lanciano R.: "Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma". *Cancer,* 2008, *112,* 1954.

[7] Committee on Practice Bulletins-Gynecology. ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas, number 35, May 2002. *Obstet. Gynecol.,* 2002, *99*, 855.

[8] Oncoguía SEGO. Cancer de cuello uterino 2008. Available at http://www.sego.es/Content/pdf/CervixOncoguia2008.pdf

[9] Hertel H., Köhler C., Elhawary T., Michels W., Possover M., Schneider A.: "Laparoscopic staging compared with imaging techniques in the staging of advanced cervical cancer". *Gynecol. Oncol*., 2002, *87,* 46.

[10] Zanvettor P.H., Filho D.F., Neves A.R., Amorim M.J., Medeiros S.M., Laranjeiras L.C.: "Laparoscopic surgical staging of locally advanced cervix cancer (IB2 to IVA): initial experience". *Gynecol. Oncol*., 2011, *120,* 358.

[11] Stehman F.B., Bundy B.N., DiSaia P.J., Keys H.M., Larson J.E., Fowler W.C.: "Carcinoma of the cervix treated with radiation therapy: a multi-variate analysis of prognostic variables in the Gynecologic Oncology Group". *Cancer,* 1991, *67*, 2776.

[12] Gien L.T., Covens A.: "Lymph node assessment in cervical cancer: prognostic and therapeutic implications". *J. Surg. Oncol*., 2009, *99*, 242.

[13] Bipat S., Glas A.S., Van Der Velden J., Zwinderman A.H., Bossuyt P.M., Stoker J.: "Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review" (Review). *Gynecol. Oncol*., 2003, *91*, 59.

[14] Yang W.T., Lam W.W., Yu M.Y., Cheung TH, Metreweli C.: "Comparison of dynamic helical CT and dynamic MR imaging in the evaluation of pelvic lymph nodes in cervical carcinoma". *Am. J. Roentgenol*., 2000, *175,* 759.

[15] Choi H.J., Roh J.W., Seo S.S., Lee S, Kim J.Y., Kim S.K. *et al*.: "Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: A prospective study". *Cancer,* 2006, *106,* 914.

[16] Sugawara Y., Eisbruch A., Kosud S., Recker B.E., Kison P.V., Wahl R.L.: "Evaluation of FDG-PET in patients with cervical cancer". *J. Nucl. Med*., 1999, *40,* 1125.

[17] Schawarz J.K., Siegel B.A., Dehdashti F., Grigsby P.W.: "Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma". *JAMA,* 2007, *298,* 2289.

[18] Perry W.: 'Grigsby. The prognostic value of PET and PET/CT in cervical cancer". *Cancer Imag*., 2008, *8,* 146.

[19] Kizer N.T., Zighelboim I., Case A.S., Dewdney S.B., Thaker P.H., Massad L.S.: "The role of PET/CT in the management of patients with cervical cancer: Practice patterns of the members of the Society of Gynecologic Oncologists". *Gynecol. Oncol.,* 2009, *114*, 310.

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